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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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IP DEPARTMENT OF PIPER RUDNICK LLP
3400 TWO LOGAN SQUARE
18TH AND ARCH STREETS
PHILADELPHIA, PA 19103

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	14

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,723	DANIELL ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-59* is/are pending in the application.

4a) Of the above claim(s) *5,8,10-14 and 21-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The claims submitted with the response filed 21 July 2003 have been entered. Claims 1-8 and 10-59 are pending. Claims 5, 8, 10-14 and 21-59 are withdrawn. Claims 1-4, 6-7 and 15-20 are examined.

2. This application contains claims 5, 8, 10-14 and 21-59 drawn to inventions nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The drawings filed 21 July 2003 are objected to because the lettering in Figures 1A, 2A-B, 8, 12-15 and 18A-B is illegible and because the details of the photographs of Figures 3, 5-7 and 9-11 cannot be made out. Corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. See 37 CFR 1.85(a) and MPEP 608.02(b).

5. The abstract is still not descriptive of the instant invention, which is a plastids transformation vector encoding a Bt crystal protein and a chaperonin. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

6. The title of the invention is still not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

Claim Objections

7. Claim 15 remains objected to and claim 1 is objected to because of the following informalities:

In claim 15, --and-- should be inserted after "chaperonin" in line 5.

The following objection is new, due to amendment:

In claim 1, line 5, the comma after "vector" should be deleted.

Claim Rejections - 35 USC § 112

8. Claims 1-4, 6-7 and 15-20 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plastid transformation vector comprising the cry2Aa2 operon, does not reasonably provide enablement for a plastid transformation vector comprising any operon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1-4, 6-7, 9, 15-20 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that an operon is well-understood to relate to a cluster of genes, the products of which all serve a particular function and that are driven by a single promoter and that there must be translation of the first gene in the cluster before there is translation of the second gene; each gene must have its own ribosome binding site (RBS). Operons include, but are not limited to the lac operon, the his operon, the lacI operon the mer operon and the Cry2Aa2 operon. Applicant urges that they do not claim all multi-gene operons but claim multigene

operons that are functional to co-express multiple heterologous proteins within the plastids. Applicant urges that pg 19, lines 6-16 of the specification specifically define the types of operons that can be used in the vectors (response pg 14-15).

This is not found persuasive. Most broadly, an operon is not a cluster of genes whose products serve a related function, but is instead a cluster of genes transcribed from a single promoter. Applicant has not taught such operons within the full scope of the claims, nor has applicant taught what to do with plants transformed with such operons. Applicant has not taught even how to use plants comprise any operon whose products serve a related function. Applicant does not teach how to distinguish operons that are functional to co-express multiple heterologous proteins within the plastids from those that do not. Pg 19, lines 6-16 of the specification merely states that any of the 133 Cry or Cyt genes shown in a particular (incorrectly cited) article may be used; it does not define the operons used in the vectors of the instant invention.

Applicant urges that they have incorporated by reference WO 99/10513 describing a universal vector capable of transforming the plastid genome of different plant species, wherein the vector integrates at least two genes into the spacer region between the chloroplast tRNA genes for ile and ala within the inverted repeat. Applicant cites paragraphs from that reference (response pg 15-17).

This is not found persuasive because Heifetz, cited in the prior Office action, teaches that plastid transformation and regeneration of fertile plants with transformed plastids is limited to two plant species. Note that newly added claim is drawn to progeny of the plant; thus, fertility is required. None of the plants transformed in WO 99/10513 produced seeds and most were not regenerated into plants; thus, WO 99/10513 cannot be relied on for enablement. Additionally,

the cited paragraphs state that the spacer region may be the one between the chloroplast tRNA genes for ile and ala.

Applicant urges that at the time the instant application was filed there were at least 60 known transcriptionally active spacer regions from higher plants plastid genomes. Applicant cites Sugita et al (1996). Applicant, citing Ruf et al (2001), and Sidirov et al (1999), states that the plastids of tomato and potato have been transformed. Applicant urges that Heifetz teaches that complete plastid genomes have been sequenced and urges that this information can provide information on conservation of reading frames and regulatory sequences. Applicant lists a variety of plants and states that their genome sequences were available in GenBank at the time of filing. Applicant urges that one could simply search appropriate spacer regions of the various plastid genomes without undue experimentation (response pg 17-19).

This is not found persuasive. Sugita et al (1996), Ruf et al (2001), Sidirov et al (1999) and the Genbank sequences could not be considered because they were not sent. However, Heifetz and Ruf et al (2001) cannot be relied on for enablement because they were published after the filing date of the instant application (see *In re Glass*, 181 USPQ 31, 34 (CCPA 1974), which teaches that references published after the filing date of an application may not be relied upon for the enablement of the specification.) Furthermore, Heifetz indicates that stable plastid transformation requires regeneration of fertile plants with transformed plastids (pg 656, left column, paragraph 1) and that segregation to the homoplastic state is the factor limiting plastid transformation to solanaceous plants (pg 658, right column, paragraph 2). Knowledge of DNA sequences does not provide overcome these problems and does not enable plastid transformation.

Applicant urges that Example 18 of the Written Description Guidelines correlates with Applicant's claims relating to plastid transformation constructs and urges that example 18 is

drawn to an allowed genus even though only one embodiment was reduced to practice. Applicant urges that their invention uses the universal vector to transform tobacco plastids with multi-gene operons with a multigene that is expressed as a fully functional Bt toxin. Applicant urges that their claims are drawn to a genus by illustrating an embodiment that is representative of the genus. Applicant urges that by applying the reasoning of Example 18 any of a variety of operons Applicant described on pg 19, lines 6-16 and throughout the specification can be used (response pg 19-20).

This is not found persuasive because Example 18 of the Written Description Guidelines is drawn to Written Description, not enablement. See the Written Description rejection below.

Applicant urges that Figure 14-18 show a variety of transformation vectors capable of integrating multigene operons, and Figure 18 provides an example of species specific vectors for alfalfa, soybean, potato and tomato, which offer examples of plants whose DNA sequences were not known at the time of filing. Applicant urges that these examples teach one of skill in the art to create a species-specific vector without detailed knowledge of the plastid genome to be transformed. Applicant urges that Kanno et al is thus irrelevant in light of the knowledge relating to spacer regions (response pg 20).

This is not found persuasive because Figures 14-15 and 18 show drawings, not vector sequences. Applicant states above that the sequences were not known at the time of filing. Figures 16-17 show gels with PCR products on them, but the specification does not teach the PCR primers or conditions needed to isolate those DNAs, nor do they teach what was being isolated. Thus, given this lack of guidance, the specification does not teach how to create a species-specific vector.

9. Claims 1-4, 6-7 and 15-20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1-4, 6-7, 9, 15-20 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that Example 18 of the Written Description Guidelines correlates with Applicant's claims relating to plastid transformation constructs and urges that example 18 is drawn to an allowed genus even though only one embodiment was reduced to practice. Applicant urges that their invention uses the universal vector to transform tobacco plastids with multi-gene operons with a multigene that is expressed as a fully functional Bt toxin. Applicant urges that their claims are drawn to a genus by illustrating an embodiment that is representative of the genus. Applicant urges that by applying the reasoning of Example 18 any of a variety of operons Applicant described on pg 19, lines 6-16 and throughout the specification can be used (response pg 19-20).

This is not found persuasive. Example 18 of the Written Description Guidelines is not analogous to the instantly case. Example 18 is drawn to a method of using a vector encoding any protein; vector components are not the critical part of the method. The instant claims are drawn to vectors and plants as well as methods, and the instant vectors and methods require that the spacer regions suitable for use in the plant to be transformed. For the instantly claimed vectors, plants and methods to be described, the components of the vectors, which are critical to the

invention, must be described. They are not. The "spacer regions" are not described in terms of structure and function and multigene operons other than cry2Aa2 are also not described in terms of structure and function. Thus, the claimed plants and methods are also not described.

Applicant urges that pg 19, lines 6-16 describe multigene operons and refers to pg 12 of the response (response pg 20).

This is not found persuasive. Pg 12 of the response is drawn to amendment of the abstract. however, pg 14-15 of the response do discuss operons, and those remarks will be addressed here. Most broadly, an operon is not a cluster of genes whose products serve a related function, but is instead a cluster of genes transcribed from a single promoter. Applicant has not described such operons within the full scope of the claims, nor has applicant described what to do with plants transformed with such operons. Applicant has not described even how to use plants comprise any operon whose products serve a related function. Applicant does not describe how to distinguish operons that are functional to co-express multiple heterologous proteins within the plastids from those that do not. Pg 19, lines 6-16 of the specification merely states that any of the 133 Cry or Cyt genes shown in a particular (incorrectly cited) article may be used; it does not describe the operons used in the vectors of the instant invention.

10. Claims 1-4, 6-7 and 15-20 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 7 January 2003, as applied to claims 1-4, 6-7, 9, 15-20 and 60, due to amendment of the claims. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Claim 1 is indefinite in its recitation of "flanking DNA sequences which are homologous to DNA sequences in a spacer region of the plastid genome".

Applicant, in response to a similar rejection, urges that a spacer sequences is well understood and defined in the art in publications such as WO 99/10513 and Kota et al as the region between the functional genes of a plastid genome (response pg 21).

This is not found persuasive. What level of homology do the flanking sequences have to the DNA sequences?

The following rejections are new, due to amendment:

Claim 1 is indefinite in its recitation of "flanking each side of the vector" in line 11. A vector is generally a circular molecule. How can DNA sequences flank a circular molecule?

Claim 15 lacks antecedent basis for the limitations "The method" in line 1 and "the selected plant" in line 4.

Claim 16 lacks antecedent basis for the limitation "the plant which allows the expression" in lines 1-2 and "said insecticidal protein" in line 2.

Claim 16 is indefinite for its recitation of "wherein growing the plant ... further comprises the steps of culturing said plant ... and selecting transformed plants". Selecting plants is not a growing step, but is a different step altogether.

Claim 17 lacks antecedent basis for the limitation "said transformed plant cells" in line 2.

Claim Rejections - 35 USC § 102

11. Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Blowers et al (WO 99/05265). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1 and 60. Applicant's arguments and the

Declaration of Henry Daniell, both filed 21 July 2003, have been fully considered but they are not persuasive.

Applicant urges that Blowers et al fails to provide an enabling disclosure for a vector capable of integrating a multigene operon into the plastid genome. Applicant urges that Blowers et al states that blot analysis of the transformants should reveal that the expression cassette was integrated. Applicant urges that the construct was merely a prophetic example that showed no tangible proof that the entire operon was integrated and expressed (response pg 21-22).

This is not found persuasive. Bowers et al do teach that the operon was expressed in cells, calli and plants. Pg 56, line 14, to pg 57, line 8, teach that the construct successfully resulted in hph phosphotransferase activity and glyphosate resistance. Thus, Blowers it do show that the operon was integrated and expressed.

Applicant urges that example 2 of Blowers et al merely provides expression of hph and not the expression of a stoichimetric ratio of *hph* and *aad* and not of Blowers indicate where and whether the genes of the constructs were expressed in a stoichimetric ratio (response pg).

This is not found persuasive. The rejection is made because the Examiner cannot determine whether the prior art possesses the unrecited characteristics. Where the prior art product seems to be identical, except that the prior art is silent to a characteristic or property claimed, then the burden shifts to Applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. See *In re Best* 195 USPQ 430, 433 (CCPA 1977).

In response to applicant's arguments, the recitation "expressing said multiple genes in a substantially stoichimetric ratio" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it

merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Applicant urges that Ana Bailey, a co-inventor of the Blowers patent was a visiting professor in Prof. Daniell's laboratory and that an abstract to a meeting was submitted. However, in spite of repeated efforts expression of the glpA/B operon was unsuccessful and the abstract withdrawn. The Declaration of Henry Daniell reiterates this (response pg 22 and Declaration).

This is not found persuasive because of the data presented in Blowers et al, as discussed above. The patent of Blowers was not publically retracted for lack of enablement. Furthermore, the *glpA/B* operon is different than the *glpB-hph-aadA* construct of Blowers et al, and thus, lack of expression of the *glpA/B* operon does not provide evidence of lack of enablement of an operon comprising *glpB-hph-aadA*.

Claim Rejections - 35 USC § 103

12. Claims 1-3, 6-7 and 15-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kota et al (1999, Proc. Natl. Acad. Sci. USA 96:1840-1845) in view of Daniell et al (1994, NATO ASI Series, Vol H 86, Biochemical and Cellular Mechanisms of Stress Tolerance in Plants, Cherry, ed., Springer-Verlag, Berlin). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1-3, 6-7, 9, 15-20 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that while Daniell et al speculated that cry operons may be expressed in chloroplasts, this would not have been possible based on the chloroplast vectors illustrated in that publication. Applicant also points out that the vectors in Daniell et al do not contain all the elements of the claimed vectors (response pg 23).

This is not found persuasive. Kota et al provided the enabling chloroplast transformation vectors, which contain the general chloroplast transformation vector elements required in the claims.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant urges that *In re Lee* states that the motivation for combining references must be specific, and the reasons one of ordinary skill in the art would have been motivated to select the references and combine them must be explained (response pg 23-24).

This is not found persuasive because Kota et al, on pg 1844, left column, states "the entire *cry*2Aa2 operon should be expressed in chloroplasts, because chloroplasts routinely express and process polycistrons (33)", where reference 33 is Daniell et al. Thus, Kota et al provides the specific motivation to combine these two references.

Applicant urges that the Office action fails to provide evidence to suggest that it was possible to express a prokaryotic Bt operon as described in Daniell in the vectors disclosed by Kota et al. Applicant urges that Kota et al does not disclose vectors comprising a chaperonin coding sequence and fails to show the introduction of multiple genes in a single transformation event. Applicant urges that Kota et al merely makes a prophetic statement that the entire

Cry2Aa2 operon should be expressed in a chloroplast simply because a chloroplast can express and process a polycistron (response pg 24-25).

This is not found persuasive. Kota et al do show the introduction of multiple genes in a single transformation event; the vector they used to transform tobacco comprises the *aadA* and the *cry*2Aa2 genes expressed from a single promoter, *Prrn* (pg 1842, left column, paragraph 1 and Fig. 1A).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., vectors comprising a chaperonin coding sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant urges that several unique requirements should be fulfilled to achieve expression of a heterologous operon in transgenic chloroplasts, including large fragment of foreign DNA should be integrated; prior to the instant invention a maximum of only two foreign genes had been integrated into plastid genomes and there was uncertainty about the maximal size for integration of foreign genes.

This is not found persuasive. Applicant provides no evidence to back up this assertion, and certainly neither Kota et al nor Daniell et al anticipated any problem expressing an operon in plastids.

Applicant urges that there was uncertainty whether a heterologous operon could be transcribed by a chloroplast promoter because other foreign promoters are non-functional within plastids (response pg 25).

This is not found persuasive. A foreign promoter is unnecessary because a chloroplast promoter would be used, as Kota et al used the *Prrn* promoter (pg 1842, left column, paragraph 1). Furthermore, in that paragraph Kota et al state that the protein synthetic machinery is similar between chloroplasts and *E. coli*.

Applicant urges that there was uncertainty whether heterologous intergenic spacer regions would be recognized by chloroplast ribonucleases and foreign transcripts accurately processed for translation; Applicant urges that polyproteins would need to be processed by chloroplast proteases (response pg 25).

This is not found persuasive because this is not the way operons work. An operon consists of several open reading frames expressed from a single promoter; each open reading frame has a ribosome binding site before it. The open reading frames are transcribed as a single RNA, and ribosomes independently translate each open reading frame. Polyproteins are not made by operons, and thus do not need to be processed. Furthermore, Applicant's arguments contradict their statement on pg 25, paragraph 1, of the response, which states that chloroplasts can express and process a polycistron.

Applicant urges that after processing, proper ribosome binding sites (RBSs) should be present that would facilitate binding of chloroplast ribosomes and initiate translation. Applicant urges that chloroplast genes contain such RBSs located exactly 5 nucleotide upstream of the start codon, and variation of this distance or sequence negatively affects efficiency of translation (response pg 25-26).

This is not found persuasive. Kota et al demonstrate that the RBSs in the cry2Aa2 operon function in tobacco plastids because a large quality of the Cry2Aa2 protein was produced in leaves (pg 1842, right column, paragraph 2).

Applicant urges that in addition to the RBS, "it was uncertain that foreign transcripts would be unstable in the absence of chloroplast 3' UTRs" [sic] and that none of the genes in heterologous multigene operons contained 3' UTRs. Applicant urges that none of the enzymes or proteins involved in this process have been characterized and they are expected to be nuclear encoded that thus, their recognition of foreign nucleotide or amino acid sequences is highly questionable (response pg 26).

This is not found persuasive because one of skill in the art would use a plastid 3' UTR in the construct, as did Kota et al (pg 1842, left column, paragraph 1). One of skill in the art would know that the 3' UTR only needs to be at the end of the operon, not after each open reading frame.

Applicant urges that after translation the heterologous proteins should be present in proper ratios to assemble the cubidal crystals and neither should be degraded by chloroplast proteases (response pg 26).

This is not found persuasive because Kota et al teach that the cry2Aa2 produced in tobacco chloroplasts is functional (pg 1843); thus, they demonstrate that chloroplast proteases are not a concern. The claims are not drawn to the production of cubidal crystals.

Applicant urges that formed cuboidal crystals in transgenic chloroplasts should not destabilize the chloroplast thylakoid membranes and negatively impact photosynthesis or growth of transgenic plants; thus, accomplishing expression of foreign operons in plastids is a much greater challenge than prior simplistic speculation and this is why the first report made the cover of Nature Biotechnology (response pg 26).

This is not found persuasive because Kota et al teach that Cry2Aa2 protein is readily expressed at high levels in tobacco chloroplasts (pg 1842, right column, paragraph 2 and

abstract). Thus, the protein does not destabilize chloroplast thylakoid membranes and negatively impact photosynthesis or growth of transgenic plants.

Applicant urges that the processing and/or cofactors necessary for processing of polycistrons via the chloroplast has not been characterized when Kota et al was published, and thus there was no evidence that multiple foreign gene transcripts would be properly processed and translated when expressed from a homologous promoter (response pg 26).

This is not found persuasive. One of skill in the art would know not use to a promoter homologous to the foreign gene but would know to use a promoter shown to function in the organism into which the construct is being transformed; Kota et al uses the chloroplast Prrn promoter (pg 1842, left column, paragraph 1). Kota et al teach that a multiple gene transcript encoding aadA and cry2Aa2 is properly processed and translated (pg 1842).

Applicant urges that the suggestion of Daniell et al to express the entire operon in tobacco chloroplasts provides no evidence as to the ability to express a multiple gene operon in chloroplasts; rather Daniell et al "states that it is desirable to express an entire operon and that it **should result in the production of stable crystalline insecticidal protein.**" Applicant urges that while Daniell et al states that the operon will be inserted and will be examined, they offer no evidence that would substantiate the likelihood of expression of a bacterial operon owing to the fact that there was an inadequate understanding of the processing of polycistrons within plastids (response pg 26-27).

This is not found persuasive. Kota et al teach that a multiple gene transcript encoding aadA and cry2Aa2 is properly processed and translated (pg 1842). Furthermore Daniell et al correctly predicted that expression of the entire operon would result in the production of stable crystalline protein.

It is noted that only a reasonable expectation of success is required for determinations of obviousness, as taught in *In re O'Farrell*, 7 USPQ 2d 1673, 1681 (Fed. Cir. 1988).

Applicant urges that up to the date of applicant's disclosure, all foreign genes engineering into the plastid genome had been driven by individual promoters and 3' regulatory regions, and urges that at the time of filing it was not known whether 3' terminator and related regulatory sequences were necessary. Applicant cites Ruiz et al (2003, Plant Physiol. 132:1-9) (response pg 27).

This is not found persuasive. As discussed above, Kota et al teach successful expression of a multiple gene transcript encoding aadA and cry2Aa2 from a single promoter, the chloroplast Prrn promoter and using a single 3' terminator (pg 1842). One of skill in the art would know to and would readily be able to put a chloroplast 3'UTR at the end of the operon. Whether 3' UTRs are necessary is thus not relevant.

Applicant urges that it was further believed that the processing of polycistrons within a chloroplast was regulated by several environmental factors such as light, and that several studies confer light dependent translation not only to psbA by with other heterologous proteins. Applicant cites Zergies et al, Eibl et al, Staub et al, 1993 and Staub et al, 1994, but did not send them (response pg 27).

This is not found persuasive. The relevance of this argument to the instant case is unclear, as no claims are directed to the use of the psbA promoter. Zergies et al, Eibl et al, Staub et al, 1993, and Staub et al, 1994, could not be considered because they were not sent.

Applicant urges that neither Kota et al nor Daniell et al suggest RBSs or untranslated regions upstream of bacterial genes could function within plastids "or processing sequences in

spacer regions"[sic]. Applicant urges that there was thus no reasonable likelihood of success (response pg 27-28).

This is not found persuasive because Kota et al, by expressing the cry2Aa2 gene in tobacco plastids, teach that its RBS functions well in those plastids. Furthermore, one of skill in the art could easily mutate its RBS to make it conform to the tobacco chloroplast RBS, as did Maliga et al (US 5,877,402, column 36, lines 32-35). No claims are directed to processing sequences in spacer regions.

Applicant urges that neither reference teaches or suggests that a chaperonin present in the bacterial cell could function within the chloroplast to help fold the foreign protein "or interfere with folding of other chloroplast proteins." Applicant urges that "[i]t is well understood in the art that *E. coli* does not form mature polypeptides, because *E. coli* does not form disulphide bonds in the cytoplasm" and to make a mature polypeptide it must be targeted to the periplasm to form disulphide bonds. Applicant urges that neither of these references suggest that it was possible to create a cubiodal crystal within a chloroplast or duplicate a bioremediation pathway within plastids; there was no reasonable predictability of success (response pg 28).

This is not found persuasive because Kota et al teach that functional cry2Aa2 is successfully produced in tobacco chloroplasts (paragraph spanning pg 1843-1844), thus, there was a reasonable expectation of success. Furthermore, Kota et al does suggest that the proteins required for folding cry2Aa2 could function in tobacco plastids and they suggest it by suggesting its expression in chloroplasts to produce crystals.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., formation of crystals) are not recited in the rejected claim(s). Although the claims are interpreted in light of

the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant urges that the prior art even suggested the potential for unforeseen deleterious effects where there is a high level of expression of multiple foreign proteins within chloroplasts. Applicant urges that because the pH and oxidation state of chloroplasts differ substantially from bacterial cells, this would inhibit or present functions of bacterial proteins and/or enzymes with the chloroplast (response pg 28).

This is not found persuasive. Applicant does not include the prior art that suggested the potential for unforeseen deleterious effects where there is a high level of expression of multiple foreign proteins within chloroplasts, and thus this is an unsupported assertion. Kota et al already teach that functional cry2Aa2 can readily be produced in tobacco plastids (pg 1842-1843).

13. Claims 1-2 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Turkec (1999, Turk. J. Field Crops 4:85-90) in view of Baumann et al (1998, J. Bacteriol, 170:2045-2050). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1-2 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that Turkec is incompatible with Applicant's disclosure. Applicant urges that Turkec is related to plastid transformation of *Chlamydomonas reinhardtii*, which is a protozoan and an algae. Applicant cites, but does not send Bold and Wynne (response pg 29).

This is not found persuasive because algae are also considered plants, albeit lower plants. Bold and Wynne could not be considered because it was not sent.

In response to applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e.*, transformation

of higher plant plastids) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant urges that the Office action assumes that because of relative DNA sequence homology between chloroplast gene of higher plants and that of *C. reinhardtii*, there would necessarily be similar integration into the chloroplast genome of higher plants, and this ignored the fact that Applicant has used spacer regions that are homologous across all higher plant species but are not homologous to regions within the plastid genome of *C. reinhardtii* (response pg 29).

This is not found persuasive because the prior Office action made no such assumption; it did not need to because the claims are not directed to a vector that transformed higher plant plastids, but merely to one that transforms plastids from any plant, higher or lower. Further, the claims merely recite "spacer regions" but neither the specification nor the claims defines this term. Also the claim does not specify the source of this region.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e.*, higher plant "spacer regions") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant cites a portion of Turkec that states that further experiments are needed to achieve stable transformation of these genes in *C. reinhardtii*. Applicant urges that thus Turkec makes no suggestion to transform the chloroplast genome of higher plants with a multigene operon (response pg 29-30).

This is not found persuasive because the claims are not drawn to stable transformation. Furthermore, Turkec suggests transforming the chloroplast genome of higher plants ("crops") with a multigene operon on pg 88, paragraph 6.

Applicant urges that Turkec on pg 86 teaches the use of multiple promoters to drive individuals genes (response pg 30).

This is not found persuasive because the additional promoters are part of the region of homology to the chloroplast genome and do not drive transcription of any portion of the operon. The promoter that drives transcription of the multigene operon is the atpA chloroplast promoter.

Applicant urges that *C. reinhardtii* has a single plastid, while higher plants have many; thus, different approaches are required for integration (response pg 30).

This is not found persuasive because the claims are not drawn to a particular approach for integration.

Applicant urges that Turkec fails to teach translation of binary toxin genes and thus provides no motivation to express an operon in a plastid. Applicant urges that Turkec merely shows that there is a complex pattern of integration of transgenes, which is not surprising because it had not been possible to translate a multitude of foreign genes in the past, even though integration and transcription were reported by several investigators (response pg 30-31).

This is not found persuasive because the claims are drawn to vectors, not to methods of producing protein in plastids.

Applicant urges that Mayfield et al (2003, Proc. Natl. Acad. Sci. USA 100:438-442) teaches that codon modification results in higher levels of protein production (response pg 31).

This is not found persuasive because the claims are not drawn to particular protein expression levels or to codon modification.

14. Claim 3-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Turkec in view of Baumann et al as applied to claims 1-2 above, and further in view of Crickmore et al (1998, Microbiol. Mol. Biol. Rev. 62:807-813). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that in view of the above, the claims are patentable over the cited references (response pg 31).

This is not found persuasive for the reasons indicated above.

15. Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al (US 5,545,817, 1996). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that McBride et al merely provides an expression construct having two unrelated genes and as a result the insertion does not produce a polycistronic mRNA. Applicant cites *Milestones* ..., which was not sent, to state that use of the second gene in production resulted in a substantial increase of toxin (response pg 31-32).

This is not found persuasive. McBride suggests expressing consecutive encoding regions as an operon (column 2, lines 55-63), which would express the genes using a single promoter and 3' UTR. *Milestones* ... could not be considered because it was not sent.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that all coding sequences within the operon be related, that use of a second gene result in increased production of Bt toxin, and processing of spacer regions) are not recited in the rejected claim(s). Although

the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant urges that nowhere in McBride et al is there an example or illustration that demonstrates a multi-gene operon expressed using a single promoter, and at most McBride et al offers an invitation to attempt such expression. Applicant cites *Amgen vs Chugai* to urge that a strategy that is "obvious to try" fails to offer any reasonable expectation of success for a strategy not used before. Applicant urges that McBride et al fails to offer a detailed teaching that could result in a reasonable expectation of success, especially in light the problems Applicant overcame to express polycistrons (response pg 32).

This is not found persuasive. The issues in *Amgen vs Chugai* are completely different that the instant issues. *Amgen vs Chugai* states that a particular nucleic acid sequence encoding a protein is not obvious over the protein sequence. This is not the instant issue, which is merely the expression of genes in plastids. The claims do not recite any special element involved required to overcome any problems Applicant found in expressing polycistrons.

16. Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (US 5.877,402, 1999). The rejection is repeated for the reasons of record as set forth in the Office action mailed 7 January 2003, as applied to claims 1 and 60. Applicant's arguments filed 21 July 2003 have been fully considered but they are not persuasive.

Applicant urges that Maliga et al merely introduced a single transgene with exhibits readthrough to a native gene, which has been previously demonstrated in the literature. Applicant urges that Maliga et al presents evidence that expression of promoterless gus is highly variable compared to rbcl such that the invention would be of no value in expressing multi-subunit proteins or enzymes in a pathway (response pg 33).

This is not found persuasive because Maliga et al provides evidence that a single promoter is sufficient for transcription of multiple genes.

Applicant urges that nothing in Maliga et al suggest that there were RBSs upstream of individual cistrons contained within the vector or processing of heterologous spacer ergions (response pg 33).

This is not found persuasive because Maliga et al in column 36, lines 32-35 teach construction of RBSs for open reading frames. Processing of spacer regions is not required, as discussed above.

Applicant urges that Maliga et al did not achieve stoichimetric amounts of transcript owing to the fact that readthrough is a random event and thus coordinated expression is not possible (response pg 33).

This is not found persuasive. The teachings of Maliga et al in columns 61 and 62 combined with the teachings of column 65, lines 19-39, are sufficient for one of skill in the art to make the claimed vectors.

In response to applicant's arguments, the recitation "expressing said multiple genes in a substantially stoichimetric ratio" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
September 25, 2003

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600